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## **SPHN/PHRT: forming a Swiss-wide infrastructure for data-driven sepsis research**

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**Abstract:** Sepsis is a highly heterogenous syndrome with variable causes and outcomes. As part of the SPHN/PHRT funding program, we aim to build a highly interoperable, interconnected network for data collection, exchange and analysis of patients on intensive care units in order to predict sepsis onset and mortality earlier. All five University Hospitals, Universities, the Swiss Institute of Bioinformatics and ETH Zurich are involved in this multi-disciplinary project. With two prospective clinical observational studies, we test our infrastructure setup and improve the framework gradually and generate relevant data for research.

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# SPHN/PHRT: Forming a Swiss-Wide Infrastructure for Data-Driven Sepsis Research

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**Abstract.** Sepsis is a highly heterogeneous syndrome with variable causes and outcomes. As part of the SPHN/PHRT funding program, we aim to build a highly interoperable, interconnected network for data collection, exchange and analysis of patients on intensive care units in order to predict sepsis onset and mortality earlier. All five University Hospitals, Universities, the Swiss Institute of Bioinformatics and ETH Zurich are involved in this multi-disciplinary project. With two prospective clinical observational studies, we test our infrastructure setup and improve the framework gradually and generate relevant data for research.

**Keywords.** SPHN, personalized health, sepsis, big data, diagnostics, digital biomarker, -omics biomarkers, machine learning, data exchange, interoperability, interconnected.

## 1. Introduction

Sepsis is a highly complex, life-threatening syndrome that develops when the bodies' immune response to an infection causes injury to its own tissues and organs. The course and outcome of sepsis is highly heterogeneous and depends on complex host-pathogen interactions, the pathogen, and timing of diagnosis and effective treatment [1, 2]. Patients at risk for sepsis may benefit from personalized diagnostic assessment and treatment strategies. Multiple attempts have failed to develop classical biomarkers from e.g. serum to diagnose sepsis – also due to the heterogeneity of presentation. Digital biomarkers in sepsis may offer a different approach, as the collection of very large datasets allows to integrate time-series data of directly measured physiological parameters [3]. Within an integrative approach, digital biomarkers may be combined with -omics biomarkers (e.g. metabolomics, metagenomic, whole genome sequencing of bacteria, immune phenotyping) and form hybrid biomarkers with higher sensitivity and specificity. The use of novel machine-learning based algorithms to explore such datasets may help to better understand the data and discover patterns within the data linked to particular clinical phenotypes [2]. These algorithms may potentially allow to guide tailored personalized treatment strategies in sepsis. We aim to build a network for data-driven and -omics technology-based research to (i) recognize sepsis at an earlier stage and (ii) predict risk of mortality.

## 2. Methods

In the driver project funded by the Swiss Personalized Health Network (SPHN) and Personalized Health Related Technologies (PHRT), each University Hospital (Basel, Bern, Geneva, Lausanne and Zurich) and University of Bern and Zurich will provide data from critically ill patients hospitalized in intensive care units (ICUs).

The locally generated data is collected from various hospital information systems (IS) such as clinical and laboratory IS, devices such as ventilators and dialysis machines, ICU monitors, and treatment-related data, e.g. drug doses and transferred and stored in local clinical data warehouses (CDWH). In order to follow Sepsis 3.0 criteria [4], we regularly tag patient with suspected sepsis and collect information in the clinical IS. This will allow to compute Sepsis-3 criteria and compare data patterns to this international accepted definition of sepsis. The data is structured and interoperable between centres following SNOMED CT and LOINC ontologies. Data is then transferred in a resource description framework (RDF) format after encoding and encryption via the BioMedIT nodes to the ETH domain for further analysis. A shared data model will be used for machine-learning based analysis. The legal and governance framework is established using a Data Transfer and Use Agreement (DTUA) and Consortium Agreement (CA) [Figure 1].

The clinical outcomes of our study include: (i) prediction of sepsis with new markers in comparison to Sepsis-3 criteria and (ii) prediction of in-hospital mortality. There are two prospective observational trials conducted with these patients.

Study A includes every patient admitted to an ICU. Following specific inclusion/exclusion criteria, we include sepsis (cases) and non-sepsis (controls) upon entry of the ICU. Of all patients with an ICU admission also available pre/post-ICU data will be integrated into the data analysis. We will compare data patterns between cases and controls in regards of the previously defined outcomes.

Study B includes a subgroup of the patients from Study A. In all five hospitals a total of 300 patients with severe community acquired pneumonia (cases) and 100 patients with a severe systemic inflammation (controls) will be included. We will collect additional patient material such as serum, whole blood for DNA and RNA, respiratory and stool material, immune cells and bacterial isolates. These samples will be in-depth characterized using metabolomics, metagenomics, whole genome sequencing and immune phenotyping technologies. Digital and -omics data will then be merged and analysed to form hybrid biomarkers. Again, case and control patients will be compared in regards of the previously defined outcomes.

### 3. Results

For the digital biomarker project (Study A) we have obtained ethical approval to collect data from 15,000 ICU patients from participating centres over the next few years. In addition, a data transfer and use agreement as well as a consortium agreement have been generated. The legal process to allow data sharing was complex and involved a multiple round assessment and discussion of the legal framework with various stakeholders.

A list of clinical, physiological and laboratory variables, covering more than 500 attributes of interest was generated and linked to ontologies such as time points, application route and dosage of specific drugs, etc. Collection of data has started at local levels with a total of already several hundred patients from the participating ICUs. Within the next 6 months, we expect data from 3,000 patients to be collected.

Data transfer and exchange protocols are currently tested with all CDWH, BioMedIT, and ETH domain teams and continuously improved.

The second -omics biomarker project (Study B) has not yet started. The ethical proposal has been submitted and decision is pending. Study preparation are progressing at all centers. In regards of the sample management different biobank information management software (BIMS) systems have been established in the various centers.

### 4. Conclusions

Ethical and legal frameworks are critical in a data-driven large consortium and this bottleneck should not be underestimated. The legal discussions show a different momentum, content and motivation compared to research questions. This should be anticipated in such a project. A lead legal institution may be a good concept to provide legal advice, besides the availability of the DTUA and CA. The legal situation of large healthcare project is complex and requires a professional support. There is a clear benefit of regular meetings with all stakeholders for in-depth discussions and finding solutions for challenges. Once fully functional, the current framework will allow to collect and store data for research purposes across all Swiss University Hospitals ICUs – beyond sepsis.

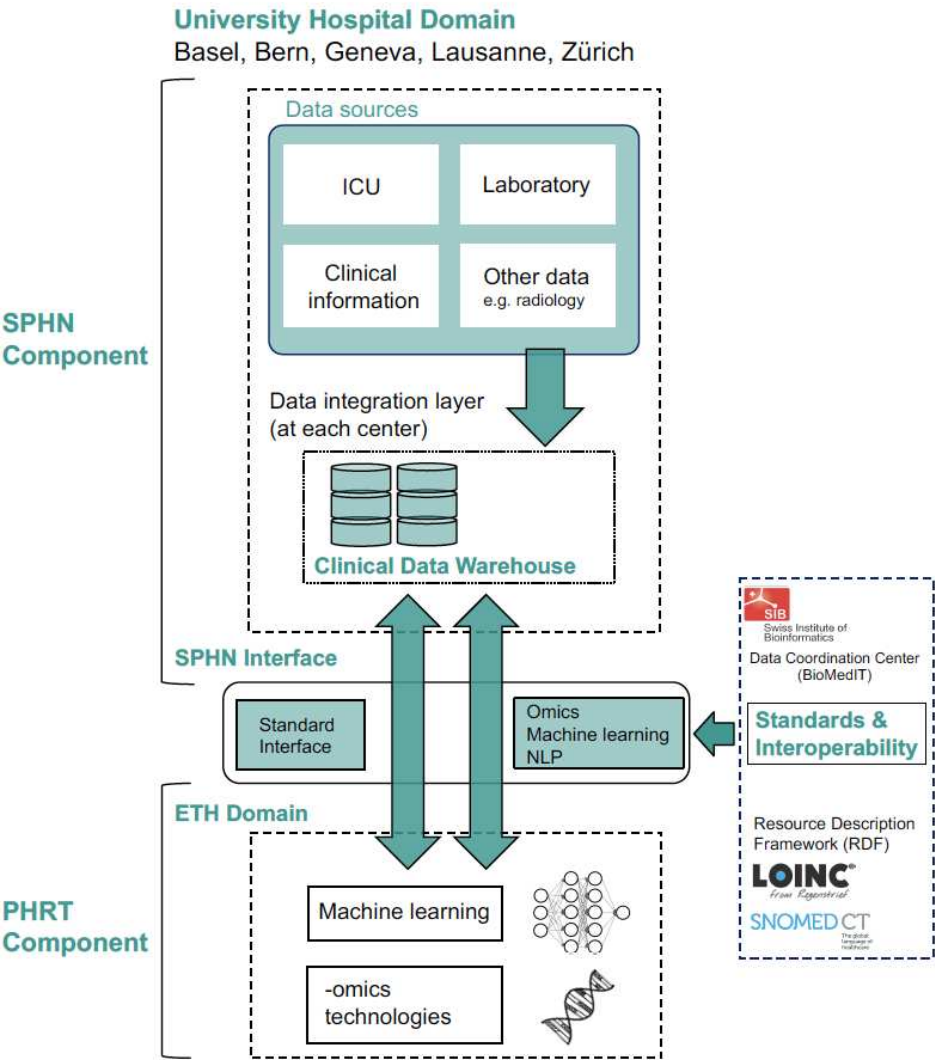


Figure 1. SPHN/PHRT framework for the Sepsis driver project. All centers locally collect data from different primary sources in clinical data warehouses. The is high interoperable and standardized following ontologies. The exchanged follows secured routes of BioMedIT to the ETH Domain for quality control and analysis. [1]

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